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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/053,871	04/01/98	PINSKY	D 51917-B

HM22/1007

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EXAMINER	
DECLOUX, A	
ART UNIT	**PAPER NUMBER**
1644	6

DATE MAILED: 10/07/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/053,871	Pinsky et al
Examiner	**Group Art Unit**
Amy DeCloux	1644

☒ Responsive to communication(s) filed on *Jul 29, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-32* is/are pending in the application.

Of the above, claim(s) *1-28, 31, and 32* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *29 and 30* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☒ The drawing(s) filed on *Apr 1, 1999* is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to Comply with Requirements for Sequence Disclosures

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1644.

2. Claims 1-32 are pending.

Applicant's election with traverse of Group III and the species muteins (claims 29-30) in Paper No. 5 is acknowledged. The traversal is on the ground(s) that the examiner has found the inventions to be distinct without also finding to be independent inventions and argues that inventions must be distinct and independent. This is not found persuasive because this is not true, that is, the MPEP clearly shows that the inventions must be independent (see MPEP 802.01, 806.04, 808.01) OR distinct as claimed (see MPEP 806.05-806.05(I))) and because the inventions require non-coextensive searches. The Inventions require different ingredients, process steps and endpoints and the species are distinct because their structures and modes of action are different inventions. Therefore, they are patentably distinct. Also, it is noted that applicant's specification is set forth as distinct and independent inventions as it relates to the different methods related to ischemia.

The traversal is on the ground(s) that the examination of the entire application would not constitute a burden to search. This is not found persuasive because, contrary to applicants' assertion that any search of the prior art in regard to groups III will reveal whether any prior art exists as to the subject manner defined by the claims in any one of Groups I, II, and IV, a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-28 and 31-32 have been withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected inventions.

3. The IDS filed 9/21/98 (Paper No. 4) refers to documents contained in the parent application Serial No. 08/721,447, all of which are available to the examiner except the following one document; Benedict, C. R., et al. (1994) "Endothelial-Dependent Procoagulation and Anticoagulation Mechanisms." Texas Heart Journal, 21:86-90. Examiner would appreciate the applicant's supplying another copy of the Benedict document, and apologizes for any inconvenience.

4. This application has been filed with informal drawings which are acceptable for examination purposes only. Accordingly, they have not been reviewed by a draftsperson at this time. When formal drawings are submitted, the draftsperson will perform a review. Formal drawings will be required when the application is allowed. Direct any inquiries concerning drawing review to the Drawing Review Branch (703) 305-8404.

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide And/Or Amino Acid Sequence Disclosures.

Applicant is required to identify all such nucleotide and amino acid sequences in the specification with SEQ. ID NOS., including those sequences disclosed on pages 20 and 21 of the instant specification.

6. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. "BALB/c" is the proper designation of this mouse strain. The use of the trademarks (ie DeToxi-gel columns on page 63 of the instant specification) have been noted in this application. It should be capitalized or accompanied by the ™ or ® symbol wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

7. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 29-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There appears to be insufficient evidence that applicant's reliance on the mouse model of cerebral ischemia and reperfusion would indicate that the claimed therapeutic modalities based upon the administration of mutants of Factor IXai would be effective to inhibit clotting but not significantly impair hemostasis, commensurate in scope with the claimed invention.

Animal model studies have not correlated well with in vivo results in patients. Since the therapeutic indices of biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the in vivo experimental mouse models accurately reflects the relative efficacy of the administration of mutants of Factor IXai in the claimed therapeutic strategy of inhibiting clotting but not significantly impair hemostasis.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

There is insufficient direction or guidance provided to assist one skilled in the art in the selection of any "inactive recombinant muteins" that are effective for inhibiting clotting but do not significantly impair hemostasis nor is there sufficient evidence provided that all such muteins are effective for inhibiting clotting but do not significantly impair hemostasis. It would require undue experimentation to produce all such possible muteins without more explicit guidance from the disclosure. It would require undue experimentation to investigate all such muteins. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the method of inhibiting of clot formation in the subject which does not significantly interfere with hemostasis when said muteins, broadly encompassed by the claims, are added to the blood administered to a patient.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a mutein's amino acid sequence and still retain the ability to inhibiting clotting but not significantly impair hemostasis, requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation. Also, minor structural differences among structurally related compounds or compositions can result in substantially different biological or pharmacological activities.

Minor structural differences among structurally related compounds or compositions, such as amino acid substitutions at one or more of the following amino acids, Ser365, Asp269, and His221 of Factor IXa, can result in substantially different biological or pharmacological activities affecting clot formation and hemostasis. Given the lack of guidance concerning the nature of the modifications associated with muteins that the skilled artisan could use as a guide in making said muteins; it would require undue experimentation to practice the claimed invention.

Applicant has failed to enable or provide sufficient guidance to those skilled generally on how to make and use all muteins that inhibit clotting but do not significantly impair hemostasis. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. It appears that undue experimentation would be required of one skilled in the art to practice all the claimed muteins that inhibit clotting but do not significantly impair hemostasis, commensurate in scope with the claimed invention using the teaching of the specification.

In view of the lack of predictability of the art to which the invention pertains, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting clotting but do not significantly impair hemostasis.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The instant claims are indefinite in that they only describe the compounds of interest by an arbitrary name , "inactive recombinant mutein". While the name itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the protein that the mutein is derived from, and variants thereof. Applicant should particularly point out and distinctly claim what is meant by inactive recombinant mutein by claiming characteristics associated with the protein (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.). Claiming biochemical molecules by a generic name fails to distinctly claim what that protein is and what the compositions are made up of. Please clarify. withdraw

B) The term "significantly interfere with hemostasis" in claim 29 is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Please clarify. withdraw

C)The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 29-30 are rejected under 35 U.S.C. § 102(b) as being anticipated by Insley et al . (US Patent 4,711,848). Insley et al. teach the mutant form of alpha-1 antitrypsin (AT) having an arginine substituted for methionine at amino acid position 358 which caused the mutant to convert from an elastase inhibitor to that of a thrombin inhibitor. Additionally, Insley et al. teach methods of making site specific mutants of AT and that altered forms of AT that could be clinically important for use in inhibiting blood clotting, as for an example, in the treatment of disseminated intravascular coagulation, (entire article, especially column lines 30-40). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations of the method of inhibiting clot formation, such as not significantly interfere with hemostasis, addressed by the applicant would be inherent properties of the referenced method using a mutated AT. withdraw

15. Claims 29-30 are rejected under 35 U.S.C. § 102(b) as being anticipated by Moller et al. (CA 2,141,642, in PTO-1449). Moller et al. teach the use of a factor IXa mutein which does not show coagulation activity and does not significantly interfere with hemostasis as a method to treat ischemic events encompassed by the claimed methods (see entire document, including pages 1-2), Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced treatment of ischemic events associated with thrombotic disease using muteins (fragments) of factors IX and IXa.

withdraw w re Factor IXa
but not with Factor IX

16. Claims 29-30 are rejected under 35 U.S.C. § 103 as being unpatentable over Moller et al. (CA 2,141,642, in PTO-1449) in view of Brandstetter et al. (PNAS 92:9796-800, 1995) and Insley et al . (US Patent 4,711,848).

The claims are drawn to a method of inhibiting clot formation in a patient, which comprises adding an inactive recombinant mutein to inhibit clot formation but which does not significantly interfere with hemostasis. Claim 30 has a further limitation wherein the patient has experienced an ischemic event.

Moller et al. teach the use of fragments of factors IX and IXa, which do not show coagulation activity as a method to treat thrombotic diseases encompassed by the claimed methods (see entire document, including pages 1-2 and 20), but do not teach specific amino acid substitutions of Factor IXa.

Brandstellar et al teach the spatial distribution of variants of Factor IXa that have been identified in clinical studies in hemophiliacs, and in particular teaches the catalytic residues SER 365 and HIS 221 that are in the active site of the serine protease(see entire document, especially page 9797, paragraph three). Inhibitory recombinant muteins of factor IXa of said two residues were referred to in the instant specification.

Insley et al teach as described above.

By Moller's teaching of treating thrombotic diseases, it would have been obvious to treat patients who have experienced an ischemic event encompassed by the claim 30 because it would have been expected that by inhibiting the coagulation cascade and thrombosis as taught by Moller et al would inhibit the vascular complications and thrombosis associated with an ischemic event. It was known at the time the invention was made that ischemia or deprivation of oxygen was due, in part, to coagulation or thrombosis and that the treatment of such conditions relied upon anti-coagulants. The dosage range and routes of administration (intravascular) were all known at the time the invention was made and would have depended upon the needs of the subject for a particular ischemic event as they read on "an amount of an inactive recombinant mutein ... effective to inhibit clot formation in the subject but which does not significantly interfere with hemostasis...".

Therefore, the ordinary artisan at the time the invention was made, would have been motivated to substitute the mutations in Factor IX found in hemophiliacs as taught by Branstellar et al, for the inhibitory fragments of factors IX and IXa taught by Moller et al, said mutations being produced according to the method of making recombinant mutants of Factor IX as taught by Insley et al., in order to accomplish a successful method of inhibiting clot formation in a subject or a patient who has experienced an ischemic event using an inhibitory factor IXa that does not significantly interfere with hemostasis taught by Moller and encompassed by the instant claims.

From the teachings of the reference and of that known and practiced by the ordinary artisan, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy DeCloux whose telephone number is (703) 306-5821. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Amy DeCloux, Ph.D.
Patent Examiner
Group 1640
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October 7, 1999

PHILLIP GAMBEL
PATENT EXAMINER
GROUP 1640

TECH CENTER 1600
10/6/99
PATENT EXAMINER

Application No.: 09/053,871

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s)

☑ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☑ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☑ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

Applicant Must Provide:

☑ An Initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☑ An Initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☑ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE

COPY FOR [ ] File [ ] Applicant